G E N E T I C C O U N S E L L I N G I N S E V E R E

O S T E O G E N E S I S I M P E R F E C T A

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ABSTRACT

Osteogenesis imperfecta (OI) is a heterogeneous group of disorders of connective tissue which principally manifest as osteoporosis and bone fragility. It is likely that monogenic defects of collagen underlie these conditions.

The present study addresses the problem of giving genetic counselling to parents of a 'sporadic' case of severe OI, either of the perinatally lethal or severe deforming variety. Such cases are likely to represent either fresh dominant mutations with no recurrence risk to sibs or autosomal recessive inheritance, with a 25% recurrence risk. Occasionally, parental gonadal mosaicism for a dominant mutation may also account for recurrences in sibs.

The main existing clinical and genetic classification of OI by David Sillence and his colleagues is extremely useful, but has limitations, due to heterogeneity within types and clinical overlap between types. Severe progressively deforming OI can be autosomal recessively inherited (Sillence type III) or autosomal dominantly determined (Sillence type IV); sporadic cases cannot be precisely allocated to either type. The present study overcomes this dilemma by pooling together a type III/IV group and determining the empirical recurrence risk to sibs. This is 4.4% (6 affected sibs out of 135 sibs of 104 cases). In these families, the parents are unrelated. In an additional 4 families, the parents are consanguineous and as there is other

evidence for autosomal recessive inheritance in these families, their disease is presumed to be recessively determined.

A source of confusion between the perinatally lethal (Sillence type II) and the severe deforming (Sillence type III/IV) categories is that the time of death may overlap. The present study suggests that a solution to this dilemma is to classify cases radiologically (rather than by time of death), as soon after birth as possible. In addition, the degree of radiological abnormality at birth can predict the prognosis, to some extent.

Originally, Sillence and his colleagues suggested that all 3 perinatally lethal types (IIA, IIB and IIC) were autosomal recessively inherited. The recurrences in sibs in the type II groups in the present series are: type IIA, no recurrences in the 38 sibs of 30 cases; type IIB, one affected sib of 13 sibs of 15 cases; type IIC, no affected sibs of the 3 sibs of 3 cases. For the type IIA group, the data support the suggestion of other authors that the majority of cases arise by new dominant mutations, and so the risk of recurrence to sibs is small. The occasional reports of sib recurrences probably can be attributed to parental germinal mosaicism. The present data and other evidence for types IIB and IIC OI means that autosomal recessive inheritance still cannot be ruled out.

Detailed clinical, radiological and family data are included in order to demonstrate the manifestations in the various types of OI to which the recurrence risk figures apply. No reliable

distinguishing features between the sporadic and familial cases of severe deforming OI (type III/IV) are found. It is not possible to pinpoint parents as being heterozygotes for recessive forms of OI on clinical grounds.

The outcome of collaborations with colleagues in molecular genetics and biochemistry are described.